MYERS BIGEL SIBLEY & SAJOVEC
Patent Attorneys
4140 Parklake Avenue, Suite 600, Raleigh, NC 27612
P.O. Box 37428, Raleigh, NC 27627
919-854-1400
Facsimile 919-854-1401

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To: **Examiner Shengjun Wang**

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Regarding USSN 09/465,429: In connection with the Request for Reconsideration filed March 31, 2004, attached is a signed copy of the "Declaration of Dr. Richard C. Boucher, Jr., Under 37 C.F.R. §1.132".

CERTIFICATION OF FACSIMILE TRANSMISSION UNDER 37 CFR 1.8

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Susan E. Freedman

Susan E. Freedman
Date of Signature: April 13, 2004

Attorney Docket No. 5470-250

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Boucher, Jr.
Serial No.: 09/465,429
Filed: December 21, 1999
For: *COMPOUNDS AND METHODS FOR THE TREATMENT OF AIRWAY DISEASES AND FOR THE DELIVERY OF AIRWAY DRUGS*

Confirmation No. 8856
Group Art Unit 1617
Examiner: Shengjun Wang

March 31, 2004

Commissioner for Patents
Post Office Box 1450
Alexandria, Virginia 22313-1450

Declaration of Dr. Richard C. Boucher, Jr. Under 37 C.F.R. § 1.132

I, Richard C. Boucher, Jr. do hereby declare and say as follows:

1. I am the inventor on the above-referenced patent application and am familiar with the contents thereof.

2. I have extensive experience in pulmonary and critical care medicine. I received my B.A. from Yale University in New Haven, Connecticut in 1966. I received my M.D. from Columbia University College of Physicians and Surgeons in New York, New York in 1970. In 1972, I participated in a residency program at Columbia Presbyterian Hospital in New York, New York. In 1977, I served as a fellow at Royal Victoria Hospital in Montreal, Canada. I am currently a Professor of Medicine and the Director of the Cystic Fibrosis/Pulmonary Research and Treatment Center at the University of North Carolina at Chapel Hill School of Medicine, where I hold an endowed chair as a William Rand Kenan Professor. I am also a recipient of the Doris Tulcin and Paul Di Sant'Agnese Cystic Fibrosis Research Awards.

3. Many aspects of the functions of airway epithelia in health and disease are poorly understood and remain to be elucidated. It is well known, however, that chronic obstructive pulmonary diseases are characterized by the retention of mucous secretions in the lungs. Unfortunately, treatment of such airway and/or pulmonary disorders is limited. To this end, investigations described in paragraph 5 below were carried out by myself and others affiliated with these studies in order to provide methods of administering an active therapeutic agent to an airway surface of a subject in need thereof.

4. In general, I am interested in the functions of airway epithelia in health and disease. More specifically, in this instance, I am interested in methods of administering an active therapeutic agent to an airway surface of a subject in need thereof.

5. Experiments designed to test methods of administering an active therapeutic agent to a compromised airway surface showed an increase in drug penetration associated with the methods of the present invention.

More specifically, Figure 1 illustrates studies wherein well-differentiated cystic fibrosis bronchial epithelia were loaded with 5 μM Snarf (Molecular Probes, USA) to denote the cell cytosol, red in color (Panel A). Isotonic solution (1.5 μL) was added to the apical surface of a thickened mucus layer followed by fluorescein 20 μM (green in color, Panel B). Panel B image was captured 5 min post fluorescein addition. Applicant notes that the drug surrogate was trapped in thickened mucus and access to epithelial surface (and epithelial uptake) was restricted. No cellular uptake was detectable. Applicant further notes that fluorescein was employed in this assay for the molecular weight similarity to that of amiloride (332 compared to 266, respectively,) and assists in the visualization of mucus viscosity and its significance in drug transport.

Figure 2 illustrates the same method as applied in Figure 1, except a hypertonic solution (~300 mM potassium phosphate) was added to the apical surface rather than isotonic saline. Hypertonic solution swelled the mucus, allowing the drug surrogate (fluorescein) to penetrate to the cell surface, following which there was rapid cellular uptake of the surrogate.

6. This result is unexpected because one skilled in the art would not predict the enhanced drug penetrance where it may be thought that the mucous layer would act as a barrier to drug penetration or that the drug may be transported away during mucociliary clearance.

7. In sum, through our experimentation in formulating active therapeutic agents and osmotically active compounds, we have provided methods of administering an active therapeutic agent to an airway surface of a subject in need thereof, comprising administering the active agent in an effective therapeutic amount in a vehicle, which vehicle comprises an osmotically active compound, the osmotically active compound included in an amount effective to increase the volume of liquid on the airway surface.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Richard C Boucher Jr. 4.6.04

Richard C. Boucher, Jr. Date